IN THE FORMAL PAPERS

In the Docket Number Space: Cancel "96605/13UTL" and replace with --012MUS/96605--.

REMARKS

Support for the Amendments can be found as follows: ("4 bases") Table A; (lysate) paragraphs 0061, 0062, 0138, 0148, etc; (enzyme) paragraph 0051, 0155, 0225, 0230, Table A; (mixture) 0064, 0069, 0075, 0100, 0110, 0111, 0120, etc.; (batch) paragraphs 0030,0058,0061,0143,0159,0189.

For reference, the text of page 2 and following of the Office Action is set forth below, with responses interlineated.

> *Application/Control Number: 09/994,701 Art Unit: 1633*
> *DETAILED ACTION*
> *Receipt and entry of the amendment dated 2/7/2006 is acknowledged. After entry of the amendment, claims 1-20,22-26,29-32 and 34-37 are pending. Claims 1-9, 18-20, and 26 remain withdrawn as drawn to non-elected inventions. Claims 10-17,22-25,29-32, and 34-37 are under examination.*
> *Claim Objections*
> *Claim 36 is objected to because of the following informalities: "comprising comprising" should be "comprising". Appropriate correction is required.*
> *Specification*
> *The specification is objected to as failing to provide proper antecedent basis for the claimed subject matter. See 37 CFR 1.75(d)(1) and MPEP § 608.01(0). Correction of the following is required: claim 16 recites the term "DNA and/or RNA compound" not found in the specification.*

The specification is obviously supportive of the method for either DNA or RNA. The objection thus is understood to be that the specification does not support DNA and RNA being processed together. But the specification does teach DNA and RNA being processed together, e.g. see paragraph 0059, brief description of Figure 5, in which plasmid DNA and RNA are processed together and also with degraded plasmid which comprises single-stranded DNA, as well. It is urged that this does support the claimed method processing DNA and RNA together and that the phrase DNA and/or RNA is supported in the specification.

Claim Rejections - 35 USC § 112
The following is a quotation of the second paragraph of 35 U.S.C. 112:
The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.
Claims 16, 17,29,30,36 and 37 are rejected under 35 V.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.
Claim 16 is rejected as being indefinite for failing to recite a positive process step that refers back to the preamble of the claim. In order for the claimed method to be definite in terms of the metes and bounds of the invention, the claim must recite a method step that provides for the results of the method as claimed. The preamble recites a method for purifying a "DNA and/or RNA compound", yet the method steps do not even recite such a compound being contacted with the IMAC ligand. Rather, a crude mixture comprising a "target compound" and contaminants is contacted with the IMAC ligand. Furthermore, the term "the compound", to be recovered in the last line of the claim, is ambiguous because the claim previously recites two "compounds": the DNA and/or RNA compound in the preamble, and the target compound in the first recited method step. This rejection affects all dependant claims. This is a new rejection.

Claim 16's DNA and RNA are clearly taught in the specification, as discussed under the objections to the specification, above. The DNA or RNA compound is now further identified as the DNA or RNA target compound.

Claim 36 recites a method for separating compounds, but the first method step recites passing RNA and/or DNA through an IMAC column. Therefore, it appears no compounds were ever passed through the IMAC column, thus it is unclear how they could be collected in the final method step. There is no nexus between the first method step and the preamble or final step. This rejection affects all dependant claims. This is a new rejection necessitated by amendment of the claims.

Claim 36's DNA and RNA is clearly taught in the spec. as discussed under the objections to the specification, above. For clarity Claim 36 now reads:

"....where the ligand is capable of differentially binding the "DNA or RNA" compounds;

and collecting purified samples of each "DNA or RNA" compound."

> *Claim 17 contains improper alternative language, as the claim states: "selected from the group consisting of' but proceeds to identify a Markush group with terminology. This constitutes improper Markush format. See MPEP 2173.05(h). This rejection is maintained for reasons made of record in the Office Action dated 2/8/2005. Applicants assert "or" has been amended to "and", but no such amendment can be found in the claim.[page4]*

Claim 17 is now cancelled without prejudice. Applicants' Attorney apologizes for the previous omission of the correction.

> *Claims 29 and 30 depend from canceled claim 27. No other pending claim reasonably recites the subject matter found in these claims (e.g. "poly(A) mRNA", "T-rich regions", "G-ricl1 regions"). Hence it is unclear what the subject matter of these claims might be. This is a new rejection necessitated by amendment of the claims.*

Claim 29 and 30 now depend on Claim 23 and have been amended to recite the "mixture" antecedent now in Claim 23.

> *Claim 32 recites a method to purify a crude compound "containing a non-shielded purine..or pyrimidine moiety from a mixture containing DNA and/or RNA, which comprise compounds with and without a non-shielded purine..or pyrimidine." It is unclear what comprise the "compounds with and without a non-shielded purine..or pyrimidine" in the context of the claim, as either the crude compound of the preamble or mixture containing DNA and/or RNA can be read to comprise this limitation. Furthermore, it is unclear which "compound" is to be recovered in the last line of the claim, as the term "compound" is used in the claim to recite two distinct entities: the "crude compound" of the preamble, and the "compounds with and without a non-shielded purine.or pyrimidine." Therefore, the metes and bounds of the claimed subject matter are unclear.*

Claim 32 now recites "target compound" in the preamble, and in the last line identifies the "target" compound as that to be recovered.

The following is a quotation of the first paragraph of 35 U.S.C. 112:
The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.
Claim 23 is rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for immobilized metal "ions", does not reasonably provide enablement for immobilized metal "atoms". The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention [page 5] commensurate in scope with these claims. This rejection is applied to a new claim for reasons made of record in the Office Action dated 2/8/2005.
Claim 23 recites a method for separating compounds using "immobilized metal atoms and/or ions." Claims 10, 11,21,22,24, and 25 were rejected in the previous Office Action under this statute for the same reasons which are applied here as before, i.e. the instant disclosure is not enabling for using metal atoms in the claimed methods. Claim 23 was inadvertently left out of the rejection, and hence stands rejected.

Claim 23 is now amended to delete "atoms or", and to recite the lysates or enzyme-containing feeds for the claimed method.

Claims 14, 15, and 31 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for contacting a liquid food stuff, such as a broth, with an IMAC ligand containing substrate, does not reasonably provide enablement for contacting of solid food with an IMAC ligand substrate. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims. This rejection is maintained for reasons made of record in the Office Action dated 2/8/2005, and for reasons set forth below.
Response to Arguments
Applicant's arguments filed 2/7/06 have been fully considered but they are not persuasive. Applicants assert that the foodstuff can be pretreated with a digestion enzyme, which will facilitate contact with solid food stuff. Such assertion is not convincing. Such a step is not recited in claim 14, and claim 15

and 31 only recite DNA digestion enzymes. It is unclear how DNA digestion enzymes could serve to render solid food, such as an apple, into a liquid form [Page 6] which the claimed IMAC ligand could come into contact. Hence, it is still considered that the disclosure is enabling only for liquid food stuffs.

Claims 14, 15 and 31 now recite soluble and liquid foodstuffs.

Claim Rejections - 35 USC § 102
The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:
A person shall be entitled to a patent unless
(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.
Claims 10-13,22-25, and 34-37 are rejected under 35 U.S.C. 102(b) as being anticipated by Petty (Curr. Protocols Mol. Biol., 1996). This rejection is maintained for reasons made of record in the Office Action dated 2/8/2005, and for reasons set forth below.[Page 27]
Response to Arguments
Applicant's arguments filed 2/7/06 have been fully considered but they are not persuasive. Applicants assert that: 1) the claims have been amended to recite that DNA and/or RNA is present and collected; 2) Petty is directed to protein purification, not nucleic acid purification; 3) Petty teaches performing the methods in the cold, which is not preferred in the instant methods; 4) Petty teaches addition of protein-destroying enzymes, which destroy the DNA and RNA moieties sought to be purified by the instant invention; 5) Petty teaches addition of DNAse, which would be disastrous in the instant invention; 6) Petty teaches purification only from E. Coli, whereas the instant invention uses much broader sources.
Regarding 1), 4), and 5), at the very least RNA is present in the bacterial celllysates of Petty and thus is anticipatory of the claims as amended. There is no amendment stating that [Page 7] DNA/RNA is collected, furthermore the limitation was found in original claim 12, and considered anticipated by the elution conditions taught by Petty (sentence bridging pages 11-12 of the previous Office Action). It is unclear how a protein-destroying enzyme could degrade DNA and/or RNA as asserted by applicants, and furthermore the step referenced by applicants is an addition of protease inhibitors, not proteases. The step of adding a DNase I, even if it were to degrade all DNA in the lysate, would still leave individual nucleosides and RNA available to bind to the Ni-NT A resin. Regarding 2), this point is not in dispute, however, the argument made in the

previous Office Action is that Petty inherently teaches the claimed invention. Such a finding of inherency does not require that the claimed feature be recognized at the time of invention/disclosure (see MPEP 2112). Regarding 3) and 6), there are no temperature or source limitations in the instant claims, hence the methods of Petty are still anticipatory.

The rejection of Claims 10-13, 22-25, and 34-37 as anticipated by Petty is respectfully traversed.

Petty is from Current Protocols series. Petty's discussion is entirely focused on purifying *proteins*, not nucleic acids. Petty specifically focuses on purifying proteins bearing extra histidine amino acids encoded by pieces of DNA added to the gene for the protein of interest.

Petty's Figure 10.118.1 shows DNA sequences, but they are not purified. Instead, Petty's DNA sources are used to add histidines to his proteins to which are to be purified. The section of Petty's page 10.1 1.11 marked "note" refers to another of adding these histidine codons to the protein-encoding gene.

Petty's Step 9 on page 10.11.13 adds expensive and toxic protease enzyme inhibitors. The present invention avoids the need for this undesirable requirement of Petty.

Petty's Step 11 (on page 10.) 1.13 adds a DNA-destroying DNAse enzyme. In many of the applications of the present invention, this would be disastrous.

The Petty reference [page 10.11.11-10.11.13] teaches purifying only from E. coli. The present invention claims recite a much broader

range of sources, including human clinical samples and enzymatically-synthesized mixtures.

In short, the Petty reference (like scores of other references) merely teaches the purifying of proteins, and a skilled person reading Petty would not learn anything of the present invention's valuable purifying of DNA and RNA.

Petty does not render obvious under 35 USC 103, Claims 10-13, 22-25 and 34-37

Nothing in Petty inherently or expressly teaches or even hints at treating lysates (or enzyme reaction products) to recover DNA (or RNA) having at least four unshielded organic base moieties, as recited in the present claims. Petty's nucleic acids are merely a source of annoying viscosity (page 10.11.13, step 10), they are not the valuable products to be purified.

Petty does speak of lysates, and his lysates may have the 4-unshielded base compounds in them. But Petty never speaks of recovering them. Thus Petty does not "inherently" practice the claimed invention. Petty talks only about purification of proteins genetically modified by Petty's addition of a histidine tail to create higher affinity. He also focuses on purification from E. coli lysates only, not patient samples, mammalian cells, lysates or enzymatic reaction products, as recited in the present claims.

Petty favors Ni NTA adsorbent. Applicants favor a different metal (Cu) and chelator (IDA). The original Murphy et al. paper showed that Ni is inferior to Cu. Figure 1 of the attached paper shows that NTA is inferior to IDA. So Petty teaches away from Aplicants' best mode in two different ways. Appplicants' also have other data that show that his favored Ni-NTA is probably very bad for our application. That is, the chelator-metal combination Applicants teach is unexpectedly good.

Petty includes a histidine-tailed protein in his lysates (the goal of his activity is to make and purify this). This is a difficult contaminant from Applicants' point of view, which favors purification from cells that do not make such a protein.

Petty favors a recombinant bacterial cell line, and does not teach non-recombinant mammalian or human patient cells. Applicants favor these in many applications.

One of Applicant's favored applications is the purification of polyA mRNA. This class of molecules is not present in Petty's lysates.

Petty requires adding costly (aprotinin, etc) and/or toxic (PMSF) protease inhibitors to his lysates (10.11.20). This is not required in applicants' methods, and might even reduce the efficacy of the present methods by protecting nucleases that can degrade applicants' favored target molecules.

Petty adds magnesium and DNAse (10.11.13) to degrade DNA. In many of applicants' preferred applications (plasmid and gDNA purification, and PCR assays) this would guarantee failure by destroying the molecules of interest. It also means that Petty ***never exposes intact DNA to his IMAC adsorbent.***

Petty does not inhibit the action of RNAse, which is important in many of applicants' applications. It is likely that after 3 freeze-thaw cycles that Petty's RNAse has degraded much of the RNA in the sample, implying that Petty never adsorbs the majority of his RNA onto the IMAC column, so that he cannot recover it intact for later uses

RNA adsorption is an important aspect of many of the applications of the present invention.

> *Claim 16 is rejected under 35 U.S.C. 102(b) as being anticipated by Hubert (1981). This rejection is maintained for reasons made of record in the Office Action dated 2/8/2005, and for reasons set forth below.*
> *Response to Arguments*
> *Applicant's arguments filed 2/7/2006 have been fully considered but they are not persuasive. Applicants assert that: 1) Hubert does not separate or collect DNA or RNA, but rather small mono- or dinucleotides; 2) Hubert does not recover products from the adsorbent; 3)Hubert doesn't test his procedure with shielded purines or pyrimidines; 4) Hubert does not teach how to purify nucleotides from cells or tissues.*
> *[Page 8]*
> *Regarding 1), the claim recites a DNA and/or RNA compound, not DNA or RNA. Lacking any guidance in the specification, a nucleotide is considered to be a "DNA and/or RNA compound" because DNA and RNA are made up of nucleotides. Furthermore, the preamble of the claim is treated only a statement of intended use because the method steps of the claim do not recite DNA and/or RNA. Thus, the preamble is given no patentable weight. Regarding 2), it is clearly taught that CMP and GMP are recovered from the copper affinity*

column (Figure 1 and the previous Office Action. Regarding 3) and 4), these are not limitations found in the instant claim.

To reject Claim 16 under 35 USC 102 on the basis of Hubert 1981 requires that every element of the invention be taught in that reference. But Hubert processes only monomers and dimers as shown by the subtitle of Hubert 1981: "Group separation of mono- and dinucleotides" Nucleotides (and dinucleotides) are all Hubert processes.

The present application now claims separation of molecules having at least four organic base groups, and they can be 1000 or even a million times bigger. [See Table A of the application.] Hubert 1981 worked at a time when the synthetic DNA oligonucleotides used by the present invention were not commercially available at reasonable prices. Present claims now specify the source material as a cell lysate or enzymatic reaction product mixture.

Sugars

Hubert uses the ribose forms of sugars - AMP etc., monomers of RNA. Hubert refers to: "the fractionation of AMP or GMP from their respective deoxy homologues could not be achieved (results not shown)". That is, Hubert *teaches away* from the present invention's valuable separation of DNA from RNA, though only at his level of monomers.

Double vs. single stranded-ness.

No previous workers, including Hubert '81 and Petty, have shown that double-stranded DNA or RNA do not bind to an IMAC column, so nothing contemplates the present invention's method of separation

of double-stranded DNA/RNA from single-stranded. This is a unique feature of the present invention. Stated differently, this is the concept of "shielding", which is used for the first time throughout the present specification, and does not appear anywhere in the prior art. The invention employs this new concept as the basis of separating one thing from another, e.g., mRNA from either plasmid or gDNA.

Geometry

Hubert just packs a column and runs chromatography, observing retention time.

Applicants teach geometries other than the references' simple packed column, including batch adsorption, etc. The present invention teaches affinities which are so much higher that the invention can do batch separations routinely.

For example, Figure 5 shows a series of batch adsorptions of an alkaline lysates containing plasmid and RNA. This mixture contains both single and double-stranded compounds, a mixture Hubert does not contemplate and Petty does not attempt to purify, and the Figure shows that substantial separation of plasmid from RNA is achieved in a single batch adsorption step. Additional batch steps produce further separation.

Starting Materials

Most importantly, Hubert never processes a lysate. He never shows that the separation can tolerate the presence of all the contaminants that can be present in a lysate. The present claims now recite lysates, and a number of different sources of the lysate/nucleic acid. The great commercial value of the invention is captured by specifying the

source material as "A cell lysate or enzymatic reaction product mixture".

Thus, Hurbert does not separate or collect any DNA or RNA - he uses only small mono- and dinucleotides. Hurbert cannot recover his products from his adsorbent. Hurbert cannot even test his procedure using a shielded purine or pyrimidine base group. Hurbert's small molecules cannot form double-stranded structures in which the bases would be shielded. In fact, Hubert does not teach how to purify even his small mono and dinucleotides from cells or tissues.

Finally, Hubert works at starting concentrations which are orders of magnitude higher than those of greatest interest in the present invention. New Claims 43 and 44 exploit the fact that Applicants'affinity is tighter, for our bigger molecules with many bases – Hubert affinity is around 3 millimolar. (See Fig 4 for support. for micro- and minimolar.)

So Hurbert certainly does not teach the presently claimed processes for separation of shielded from unshielded. Hubert does not even hint at the present invention's discovery of the concept of shielded and unshielded DNA or RNA having at least four base groups.

Claim Rejections - 35 USC § 103
The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.
Claim 17 is rejected under 35 U.S.C. 103(a) as being unpatentable over Hubert (1981) in view of Yarchoan (l986)(hereinafter Yarchoan-l), Yarchoan (1989)(hereinafter Yarchoan-2).
This rejection is maintained for reasons made of record in the Office Action dated 2/8/2005, and for reasons set forth below.
Response to Arguments
Applicant's arguments filed 21712006 have been fully considered but they are not persuasive. Applicants assert that:
1) Hubert is deficient (presumably for reasons asserted above)

and that the Yarchoan references do not make up this deficiency; 2) the Yarchoan references do not teach metal affinity chromatography.
Regarding 1), Hubert still applies for reasons recited above.
Regarding 2), in response to applicant's arguments against the references individually, one cannot show nonobviousness by [page9] attacking references individually where the rejections are based on combinations of references. See In re Keller, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); In re Merck & Co., 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986).

Yarchoan-1: Yarchoan, Mitsuya et al. is a medical paper from Science which describes a clinical trial of the use of ddI for therapy of AIDS. It does not speak of, or even contemplate, metal-chelate affinity purification or purification methods for any biomolecules, much less DNA and/or RNA, as now recited in the present claims. Serum uric acid was found to be *increased*. Thus. no purification occurs in Yarchoan at all. People eat the drug ddI and their blood chemistry changes a bit.

Yarchoan-2: Yarchoan, Weinhold et al. is a medical paper from The Lancet which merely describes a clinical trial of the use of AZT for therapy of AIDS. It does not speak of, or even contemplate metal-chelate affinity purification, or any purification methods for any biomolecules, much less DNA or RNA, as now recited.

The AIDS drug claims have been deleted without prejudice.

Adding Hubert to the Yarchoan references can be done only by hindsight because Hubert deals with metal affinity purification while the Yarchoan references do not mention this and the Yarchoan references deal with clinical trials (not purification) of an AIDS drug, (ddI or AZT), nothing of which is mentioned in Hubert. Thus there is no suggestion or motivation that these utterly different references be combined, and the *combination* itself is improper.

Conclusion: No claims are allowed.

Conclusion: Differences between the invention and the references are tabulated below:

Reference	Process lysate & enzyme reaction product ?	Separates compounds having 4+ Pu/Py base groups?	Separates shielded from unshielded Pu/Py base groups?
Claimed Invention	Yes	Yes	Yes
Hubert	No	No	No
Yarchoan I & II	No	No	No
Petty	Yes	No	No

None of the references, either alone or in combination, would either render the invention obvious under 35 USC 103, or anticipate it under 35 USC 102. Allowance of the Claims under the mandate of 35 USC is respectfully urged.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Michael D. Burkhart whose telephone number is (571) 272-2915. The examiner can normally be reached on M-F 8AM-5PM.
If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Dave Nguyen can be reached on (571) 272-0731. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.
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Michael D. Burkhart Examiner
Art Unit 1633
SCOTT D. PRIEBE, PH.D PRIMARY EXAMINER

The claims have been amended to improve clarity. No new matter has been added.

The one-month extension fee, the fee for 3 additional dependent claims and any other necessary (small entity) charges can be charged to USPTO Deposit Account 20-336 of Technology Licensing Co. LLC. Correspondence may be addressed to Customer No. 26830.

The Examiner is especially invited to suggest allowable subject matter on next action, and to telephone Applicants' Attorney if that would expedite prosecution and disposal of this Application.

Respectfully submitted,

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